

The Immunological Niche: Effect of immunosuppressant drugs on stem cell proliferation, gene expression, and differentiation in a model of spinal cord injury.

Grant Award Details

The Immunological Niche: Effect of immunosuppressant drugs on stem cell proliferation, gene expression, and differentiation in a model of spinal cord injury.

Grant Type: SEED Grant

Grant Number: RS1-00377

Investigator:

Name: Brian Cummings

Institution: University of California, Irvine

Type: PI

Disease Focus: Neurological Disorders, Spinal Cord Injury

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Award Value: \$595,345

Status: Closed

Progress Reports

Reporting Period: Year 2

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Grant Application Details

Application Title: The Immunological Niche: Effect of immunosuppressant drugs on stem cell proliferation, gene expression, and differentiation in a model of spinal cord injury.

Public Abstract:

Our understanding of the effect of immunosuppressive agents on stem cell proliferation and differentiation in the central nervous system is limited. Indeed, even the necessity for long-term immunosuppression to promote the survival of stem cells grafted into the "immunoprivileged" central nervous system (CNS) is unknown. Grafting multipotent stem cells into the injured CNS often results in a failure of the cells to survive. If the cells survive, often they differentiate into astrocytes, a cell-type not considered beneficial. We recently grafted human stem cells (hCNS-SC) into spinal injured mice and observed behavioral improvements coupled with differentiation of these human cells into neurons and oligodendrocytes. We also observed mouse-human synapse formation and remyelination. The mice we used lacked a functional immune system, enabling us to grafting human cells into the mice without the use of immunosuppressants. When these same cells were grafted into spinal injured rats with a normal immune system, we had to immunosuppress the animals. Exposure of these human stem cells to immunosuppressive drugs resulted poor cell survival. The cells that did survive predominantly differentiated into astrocytes. Did the immunosuppressive drugs we used alter the ability of the human stem cells to differentiate into useful cells?

All cell-based therapeutic approaches are dependent upon either immunosuppression in an otherwise normal animal or testing for proof of principal in an immunodeficient animal model. This has quite significant implications for animal experiments or human trials, where continuous immunosuppression is required to obtain successful graft survival. No one knows if there are direct effects of immunosuppressant drugs on neural stem cells.

Stem cells may also respond differently to immunosuppression depending on their "ontogenetic" age (embryonic vs. fetal vs. adult). There is a common perception that "young" ES cells will have greater potential than "older" stem cells. Stem cells isolated at different ontogenetic stages might respond differently to immunosuppression.

We predict that the immunosuppressive drugs will exert direct effects on stem cell proliferation, gene expression, and fate determination, both in cell culture and when grafted into animals with spinal cord injury. We will also test if "ontogenetic" age alters the responsiveness of stem cells.

Statement of Benefit to California:

The California Institute for Regenerative Medicine (CIRM) recognizes that the field of stem cell biology is in its infancy. CIRM has requested a broad range of research to fill in key gaps in our understanding of basic stem cell biology and the possible use of these cells as therapeutics. Grants are to be judged on impact (extent the proposed research addresses an important problem; significantly moves the field forward scientifically; moves the research closer to therapy; and changes the thinking or experimental practice in the field), quality (is proposed research planned carefully to give a meaningful result; are possible difficulties are acknowledge; does the timetable allows for achieving significant research) and innovation (to what extent the research approach is original, breaks new ground, and brings novel ideas to bear on an important problem).

We believe that the projects proposed here target several of the areas CIRM cites as beneficial to the State of California. This proposal addresses the critical area of immunosuppression and stem cell survival in animal transplantation models. Future therapies using human stem cells will have to surmount the possible rejection by the host of cells derived from another source. If traditional immunosuppressive drugs are to be used, we will need to understand whether these drugs have a direct effect on stem cell proliferation and fate determination (or differentiation). Furthermore, these projects will allow for a direct comparison of stem cells from different ontogenetic stages and the ability to improve functional outcome after spinal cord injury. Thus we may gain insight into whether embryonic derived stem cells are more useful than adult derived stem cells as a therapeutic tool.

